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Improved Metered Dose Inhaler Technique When a Coordination Cap Is Used

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Abstract

Background: Patients often experience problems using metered dose inhalers (MDIs), particularly poor coordination between inhalation start and dose actuation (TsIn: time difference between the start of an inhalation and the actuation of a dose), and fast peak inspiratory flow (PIF). We investigated if a coordination cap (CAP), with instruction to prolong inhalation, solved these problems.
Methods: Inhalation profiles [PIF, TsIn, inhalation volume (Vi), inhalation time (Ti)] of patients with stable asthma prescribed an MDI were measured using their real-life technique (MDI). Inhalation profiles were then measured with the cap fitted (MDI + CAP). These patients were then instructed to inhale through the MDI + CAP for 5 sec, and inhalation profiles measured (MDI + CAP + TRAIN). TsIn was only measured for the MDI.
Results: Resistances of MDI and MDI + CAP were 0.0135 and 0.0243 (cm $H_2O)^{½}$/(L/min), respectively. Seventy-one patients were evaluated, with mean [standard deviation (SD)] forced expiratory volume over 1 sec % predicted normal of 78.3% (21.0). Following MDI, MDI + CAP, and MDI + CAP + TRAIN: mean (SD) PIF was 155.6 (61.5), 112.3 (48.4), and 73.8 (34.9) L/min, respectively ($p < 0.001$); mean (SD) Ti was 1.60 (0.60), 1.92 (0.80), and 2.99 (1.03) sec, respectively ($p < 0.001$); and Vi was similar between stages. Twelve patients used a slow flow with the MDI alone, but only two of these patients demonstrated good coordination. With the cap in place (which ensures good coordination), the number of patients using a slow flow increased to 25 for MDI + CAP and to 50 following MDI + CAP + TRAIN.
Conclusions: The cap with its effect of increasing resistance to airflow combined with the instruction to prolong inhalation time significantly decreased the inhalation flow.

Key words: asthma, inhalation flow, device, I-Breathe

Introduction

The metered dose inhaler (MDI) has been the most widely used inhaler over the past 40 years, and the problems patients experience with correct inhaler technique are the same today as they were when the MDI was first introduced.[1–6] Although large volume spacers and an open-mouth technique have been used to help with coordination, these problems still exist.[1] It has been shown that poor MDI technique is related to poor asthma control[7,8] and hospitalization.[2] The recommended inhalation procedure for an MDI involves several steps (Table 1),[9] and of these, good coordination and a slow inhalation flow maintained for as long as possible are particularly important for achieving good asthma control.[7] Lung deposition is reduced when there is poor coordination between the actuation of the dose and the start of inhalation[10] and when a fast inhalation flow is used.[11,12] A breath hold at the end of the inhalation[11,12] and increased inhalation volume[12,13] both improve lung deposition.

Most studies assessing MDI technique use subjective methods,[1–3] but some have used more objective, electronic methods.[14–16] Only 8% of patients use a good inhaler technique with their MDI,[7] and although inhalation technique training can be useful,[7] in some cases it may have little effect,[14] or improvements are temporary.[17] Breath-actuated inhalers solve the problem of poor coordination,[10]

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Table 1. Instructions for Ideal Inhaler Technique with an MDI

Step	*Instruction*
1	Shake 4 or 5 times if suspension formulation.
2	Take the cap off the mouthpiece.
3	Prime the inhaler (refer to the PIL for specific instructions).
4	Exhale slowly, as far as comfortable (to empty the lungs).
5	Hold the inhaler in an upright position.
6	Immediately place the inhaler in the mouth between the teeth and on top of the tongue.
7	Ensure that the lips have formed a good seal with the mouthpiece.
8	Start to inhale slowly, through the mouth, and at the same time press the canister to actuate a dose.
9	Maintain a slow and deep inhalation, through the mouth, until the lungs are full of air. This should take an adult 4–5 sec.
10	At the end of the inhalation, take the inhaler out of the mouth and close the lips.
11	Continue to hold the breath for as long as possible, or up to 10 sec before breathing out.
12	Now breathe normally.
13	If another dose is required, repeat steps 4–12.

PIL, patient information leaflet.[9]

but are currently only available for the delivery of salbutamol and beclomethasone.

A flexible coordination cap, the I-Breathe (patent no. PCT/EP2011/006000), shown in Figure 1, has been designed to fit onto an MDI with an airtight seal, such that an inhalation cannot start until the canister is pressed. Pressing the canister causes slits in the coordination cap to open (as it becomes compressed), thereby allowing airflow. This coordination cap therefore converts the MDI into an inhalation co-ordinating device, by preventing inhalation prior to actuation. The coordination cap has been designed for use with existing familiar inhalers. In this prospective, investigational study, we have measured the inhalation parameters of asthma patients using an MDI to identify if these parameters change when the coordination cap is fitted. We have extended this to determine if a short training session to increase the patients' inhalation times in addition to the coordination cap helps to decrease their inhalation flow.

Materials and Methods

Patient demographics and baseline characteristics

Ethical committee approval was received from the Yorkshire and Humber Research Ethics Committee–Bradford (reference 09/H1302/64) and from the University of Huddersfield (SASEC/10/01). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.[18] Eligible patients had stable asthma, were 18–45 years old, and were prescribed an MDI. Those with an acute exacerbation, an infection, or viral illness in the preceding 4 weeks were excluded. All patients provided written, informed consent prior to participation. Patients' demographic data and medication usage were recorded. Their spirometry was measured using a ONE FLOW spirometer (Clement Clarke International Ltd., Harlow, UK), and they each completed the Asthma Control Questionnaire (ACQ).[19,20]

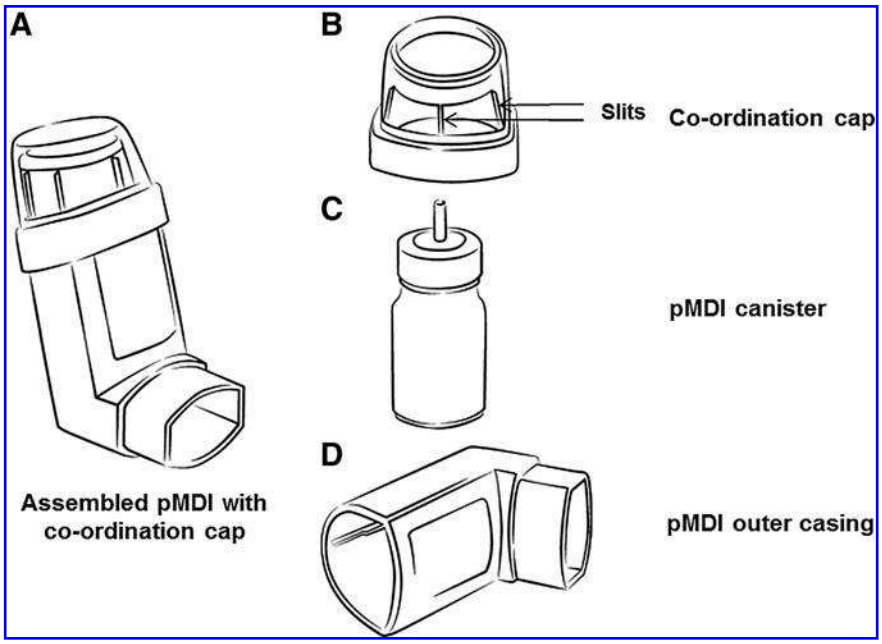

FIG. 1. The I-Breathe coordination cap. **(A)** The assembled MDI with coordination cap fitted, ready to use. **(B–D)** Components of the MDI plus coordination cap. pMDI, pressurized metered dose inhaler.

Study design and inhalation parameters

An empty MDI was adapted to enable a patient's inhalation profile to be recorded. Figure 2 describes a typical inhalation flow profile when using an MDI. The inhalation flow increases rapidly and then plateaus before falling away at the end of the inhalation. This profile shows when the point of actuation occurs after the start of inhalation. The empty MDI was encased onto the air inlet of a pneumotachograph (Cardinal Health GmbH). Flow and time measurements during an inhalation were downloaded in a Microsoft Excel spreadsheet to compute the inhalation profile. Figure 2 highlights how each profile was used to determine the study primary outcome, peak inspiratory flow (PIF; liters per minute), and the secondary outcomes, inhalation volume (Vi; liters) and inhalation time (Ti; seconds). A ratio of Vi/forced vital capacity (FVC) was calculated to indicate the depth of inhalation. The time between the start of an inhalation and pressing the canister was defined as TsIn (seconds). The inhalation time starts at the beginning of an inhalation. Figure 2 shows actuation that occurs after the start of an inhalation, and so TsIn is positive. If actuation occurred at the start of an inhalation, then this would be represented on Figure 2 as a TsIn of zero, and thus the line indicating actuation would be shown at the start of the inhalation flow. If actuation occurred before the start of an inhalation, then this line would be shown before the start of inhalation and TsIn would be negative.

Slow inhalation flow was defined as PIF of <90 L/min[11,14,21] and good coordination as TsIn of 0–0.2 sec.[14,21] A deep inhalation was defined as a Vi/FVC ratio of >0.6.[15]

All procedures were carried out during a single visit. Each patient performed the following inhalation procedures, and their inhalation profiles were measured:

- MDI alone: patients inhaled through an empty MDI using their normal day-to-day technique.
- MDI + CAP: patients inhaled through the empty MDI fitted with the coordination cap, using their normal day-to-day technique. They were informed that the coordination cap would not allow inhalation until it was depressed. Also, if they started an inhalation before actuating the canister, they would notice a vacuum that would be released when they depressed the canister. In addition, if the patient released the canister before the end of their inhalation, the slits in the cap would close and block any further inhalation through the MDI. If this did occur, the patient was instructed to keep the canister depressed until the end of their inhalation. This instruction was only given once to the patient.
- MDI + CAP + TRAIN: each patient was then trained to increase the length of their inhalation to 5 sec. This was done by the trainer demonstrating a slow inhalation while they counted to 5 and then practiced once by the patient. Patients then used the MDI fitted with the coordination cap after this training.

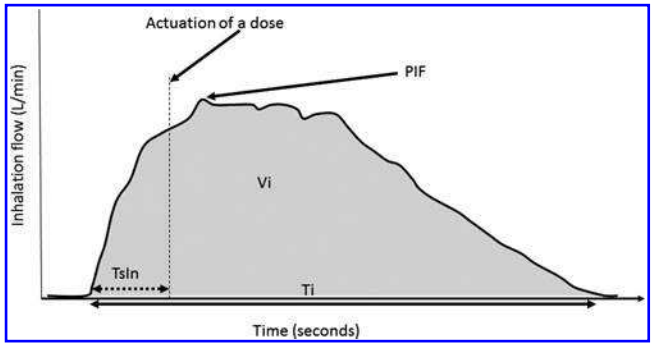

FIG. 2. An inhalation profile using an MDI measured by the inhalation profile recorder.

Each inhalation was performed twice, and the flow profile with the slower PIF was chosen for data analysis. TsIn could not be measured for MDI + CAP or MDI + CAP + TRAIN. The reason for this is because the mechanism used to measure TsIn allows a small airflow, and so would not be airtight against the MDI if the cap was in place. Such air leakage would negate the airtight seal between the MDI and the cap in the measurement system. This was therefore disconnected.

Patient satisfaction

Following the inhalations, a 5-point Likert scale was used to obtain patient satisfaction about using an MDI with the coordination cap. Patients were also asked if they perceived any advantages or disadvantages when using the coordination cap with their MDI.

Resistance of devices

The resistance of the MDI with and without the coordination cap was determined by measuring the pressure change corresponding to flows of 10–100 L/min as described by Clark and Hollingworth.[22]

Statistical analysis

A series of repeated measures analyses of covariance (ANCOVA) models was derived to assess the effect of the procedures MDI + CAP and MDI + CAP + TRAIN on the use of an MDI, with respect to the primary outcome measure of PIF and the secondary outcome measures of Vi and Ti, controlling for all measured factors and covariates [age, gender, FVC, and peak expiratory flow rate (PEFR)]. Forced expiratory volume over 1 sec (FEV_1) was excluded because it showed extreme colinearity with FVC, and hence in a regression model could lead to model instability and, in addition, its association was not as strong as FVC. All covariates were centered to avoid altering the main effect of the condition in any cases where covariate variability was large compared with condition variability. An additional series of controlled ANCOVA models was derived using the outcome measure Vi standardized by FVC. In these models, FVC was not included as a covariate.

An uncontrolled multivariate general linear model (GLM) was also performed on baseline data (MDI alone), considering the relationship between the single predictor FVC and a linear combination of the three outcome measures, with follow-up univariate models derived as appropriate.

Results

The measured resistance for the empty MDI without the coordination cap was 0.0135 (cm $H_2O)^{1/2}$/(L/min) and 0.0243

(cm $H_2O)^{½}$/(L/min) for the MDI with the coordination cap while the canister was depressed.

Seventy-one patients were recruited, and all completed the study inhalation maneuvers; their baseline characteristics and spirometry measurements are listed in Table 2. The mean [standard deviation (SD)] ACQ score was 1.32 (0.71) with 16 patients scoring <0.75, 30 patients scoring 0.75–1.5, and 25 patients scoring >1.5.

There was no statistical difference between the inhalation profiles for the slow and fast PIF recorded for each patient. Table 3 summarizes patients' inhalation parameters for the slow PIF inhalation profile recorded. For individual parameters, statistical analysis revealed pairwise differences corrected for multiple comparisons ($p<0.001$) between inhalation procedures for PIF and Ti, but not for Vi, shown in Figure 3. Table 4 shows the number of patients performing a slow (<90 L/min), fast (90–200 L/min), and very fast (>200 L/min) inhalation flow. Table 5 shows the number of patients who achieved a deep inhalation for each procedure, as determined by their Vi/FVC ratio.

With the MDI alone, TsIn values ranged from −2.40 sec (actuation before inhalation) to 1.71 sec (actuation after the start of the inhalation). Ten (14.1%) patients had a negative TsIn (TsIn −0.04 to −2.40 sec), indicating early actuation, and 25 (35.2%) patients had a late actuation (TsIn 0.24 to 1.71 sec), whereas 36 (50.7%) used the MDI with good coordination. Of these 36 patients, only two had PIF of <90 L/min; therefore, 2/71 (2.8%) demonstrated good inhalation technique with the MDI alone.

Patients were asked on a scale of 1 to 5 how satisfied they would be to use the coordination cap with their MDI in daily life (1 = unsatisfied, 5 = very satisfied). Seven patients gave a score of 3, 21 patients gave a score of 4, and 43 were very satisfied (score of 5).

The first time the MDI was fitted with the coordination cap, 17 patients had to be instructed to keep the canister depressed throughout the duration of their inhalation. The inhalation procedure was repeated, and these patients did not repeat the error for all the remaining inhalations.

An uncontrolled GLM assessing the effect of FVC on the MDI outcome measures indicated a significant association between FVC and the outcome measures assessed jointly ($\Lambda=0.651$; $F_{(3,67)}=12.0$; $p<0.001$). Subsequent follow-up univariate GLMs identified significant associations between FVC and PIF ($F_{(1,69)}=8.09$; $p=0.006$) and between FVC and Vi ($F_{(1,69)}=36.3$; $p=0.001$). The association between FVC and Ti was not statistically significant ($r=0.214$; $p=0.073$). The correlations between PIF and FVC, and between Vi and FVC, are shown in Figure 4.

Table 2. Mean (SD) Patient Demographics and Baseline Characteristics

Characteristic	N = *71*
Males, *n*	19
Age, years	32.0 (13.5)
Weight, kg	74.4 (12.8)
Height, cm	167.5 (9.7)
PEFR	
Actual, L/min	355.5 (108.1)
% predicted[23]	74.8 (23.3)
FVC	
Actual, L	3.46 (1.04)
% predicted[23]	82.4 (22.0)
FEV_1	
Actual, L	2.81 (0.85)
% predicted[23]	78.3 (21.0)

PEFR, peak expiratory flow rate.

Table 3. Mean (SD) Inhalation Parameters for Patients Using an MDI with or without the Coordination Cap

	Profile with slowest PIF			
Parameter	*MDI*	*MDI + CAP*	*MDI + CAP + TRAIN*	p *value*
PIF, L/min	155.6 (61.5)	112.3 (48.4)	73.8 (34.9)	<0.001
Vi, L	2.33 (0.84)	2.26 (0.86)	2.30 (0.79)	0.651
Ti, sec	1.60 (0.60)	1.92 (0.80)	2.99 (1.03)	<0.001
Vi/FVC	0.71 (0.22)	0.68 (0.24)	0.69 (0.21)	0.473

p values refer to controlled analysis of covariance.

Discussion

Overall, for the MDI alone, 50.7% of the patients achieved good coordination and 70.4% had a Vi/FVC ratio of >0.6, indicating a full inhalation, but only 16.9% inhaled slowly through the MDI. The proportion of patients with poor coordination was consistent with previous reports that used subjective methods,[1–3,7,24] whereas the proportion of those with good coordination and slow flow is similar to that reported in a study involving 432 asthmatics.[6] The results confirm previous studies showing that too rapid inhalation is the most common mistake made by patients.[7,24] Most patients had stable mild–moderate asthma (mean FEV_1 % predicted value of 78%), and only 16 had good self-reported asthma control (ACQ<0.75). With the cap fitted to the MDI and inclusion of a simple verbal instruction, where the patient is asked to increase inhalation duration to 5 sec, most patients could achieve a sufficiently slow inhalation flow with good coordination. As asthma control and hospitalization are related to inhaler technique,[1,7,8] use of the coordination cap and the instruction to extend inhalation to 5 sec could therefore improve technique and ultimately asthma control. These improvements could thus contribute to the challenge by the Global Initiative for Asthma to reduce hospitalizations by 50% over a 5-year period.[25]

We chose 0–0.2 sec for TsIn to represent good coordination, which is in line with that previously reported.[14] This is consolidated by the study reported by Farr *et al.*[21] In this study, medium early actuation provided greater lung deposition versus slow/early or fast/late actuation. Medium early was defined as actuation at 90 L/min when 300 mL had been inhaled, which corresponds to a time of 0.2 sec. Furthermore, as empty MDI canisters were used, any inhalation problems due to the "cold Freon effect" did not occur.[6]

The slower inhalation flow achieved with the coordination cap fitted compared with the MDI alone was due to the increased airflow resistance caused by the cap, and resulted in the slightly longer inhalation time. This suggests that new

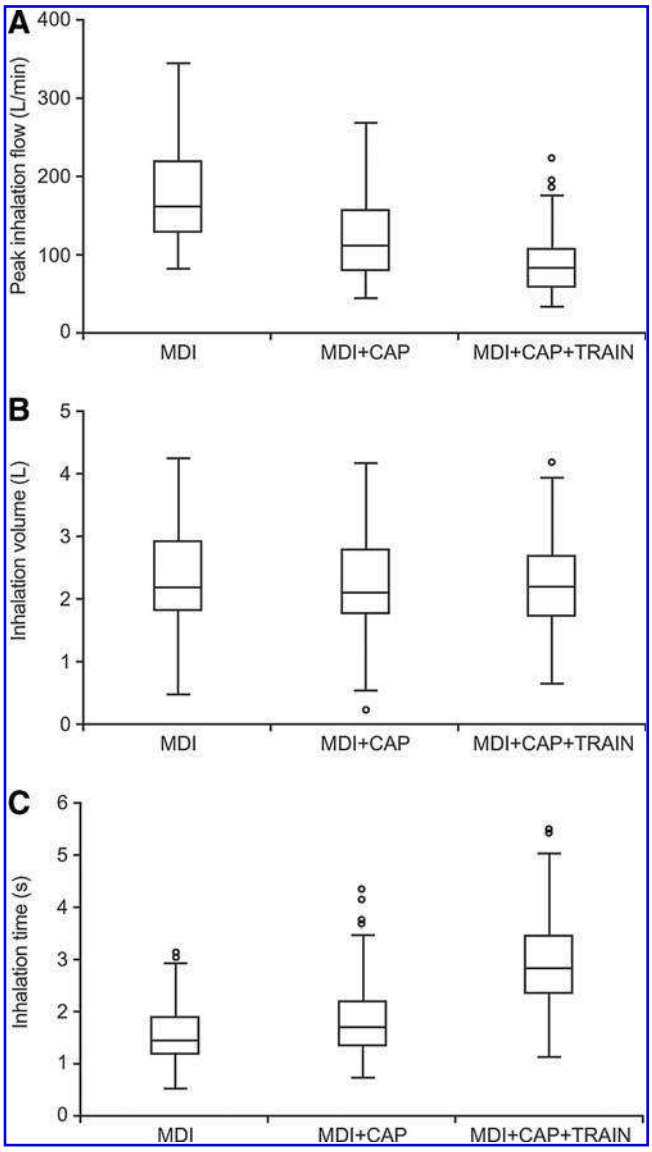

FIG. 3. Inhalation parameter distributions for the inhalation procedures, from the inhalation profile with the slower PIF recorded for each patient. Circles represent outliers. **(A)** PIF distributions. **(B)** Vi distributions. **(C)** Ti distributions. Boxes represent the interquartile range with the median, and the whiskers represent the full range of the data (excluding the outliers, which are shown as circles).

MDIs, or MDIs with new drug formulations, should be designed with more resistance to airflow to naturally reduce the speed of the inhalation flow. After the short inhalation technique training to increase inhalation to 5 sec, patient inhalation time did increase by approximately 1 sec to almost 3 sec, and as the inhalation volume was unchanged, inhalation flow was therefore decreased. Of note, this training took less than 1 min. Perhaps if more time was spent on this aspect, then patients would achieve the recommended 5-sec inhalation time,[9] and inhalation flows would be slower than those measured.

In the schematic design, presented in Figure 2, when the cap was fitted, then TsIn, theoretically, would be either zero or negative. It would be zero because inhalation is not possible until the canister is depressed; however, because the Ti measurement starts at the beginning of the inhalation flow, then if the canister was depressed before the start of the inhalation, TsIn would be negative. In this study, due to limitations of the measurement method with the cap in place, the airtight seal would be lost because of a small air leakage through the mechanism that measures TsIn. Hence, TsIn with the cap in place could not be measured. We have since redesigned the measurement method such that TsIn can be measured while maintaining an airtight system. This method is currently being used in further studies that involve patients with more severe and uncontrolled asthma who have poor MDI coordination.

Table 4. Patients Who Performed Slow (Correct) Inhalation (<90 L/min), Fast Inhalation (90–200 L/min), and Very Fast Inhalation (>200 L/min)

PIF rate, L/min	*MDI,* n *(%)*	*MDI+CAP,* n *(%)*	*MDI+CAP+ TRAIN,* n *(%)*
<90 (slow)	12 (16.9)	25 (35.2)	50 (70.4)
90–200 (fast)	41 (57.8)	42 (59.2)	21 (29.6)
>200 (very fast)	18 (25.3)	4 (5.6)	0

CAP, coordination cap; TRAIN, instruction to inhale through the MDI for a count of 5 (approximately 5 sec).

Of the duplicate inhalation maneuvers performed, the slower was analyzed.

The set of measurements using the MDI alone showed that only two (2.8%) of the patients used a slow inhalation flow with good coordination, consistent with previous observations.[7] With the coordination cap fitted (but without training), all patients would have had good coordination and 25 (35%) used a slow inhalation flow. The proportion using a slow inhalation flow increased further to 50 (70%) patients when the training (concerned with increasing the inhalation period) was included. In clinical use with the cap fitted, this would represent a large increase in the number of patients with good coordination and slow inhalation flow. Previous studies have shown the clinical benefit of a breath-actuated inhaler[26] and that poor inhaler technique is partly due to fast inhalation.[7,24] With the addition of the coordination cap, training could focus primarily on the inhalation and exhalation steps, without concerning the patient about coordination.

The I-Breathe cap works by a different principle than breath-actuated MDIs (such as Autohaler® and Easi-Breathe®),[27] as it requires the patient to depress the canister. On first use, 17 of the patients did not keep the canister depressed throughout the duration of their inhalation, causing the slits in the coordination cap to close and stop the patients from continuing their inhalation through the inhaler.

Table 5. Depth of Patients' Inhalation Measured by Vi/FVC Ratio

Vi/FVC ratio	*MDI,* n *(%)*	*MDI+CAP,* n *(%)*	*MDI+CAP+ TRAIN,* n *(%)*
<0.6	21 (29.6)	30 (42.3)	23 (32.4)
>0.6	50 (70.4)	41 (57.8)	48 (67.6)

CAP, coordination cap; TRAIN, instruction to inhale through the MDI for a count of 5 (approximately 5 sec).

Deep inhalation is defined as a Vi/FVC ratio of >0.6.

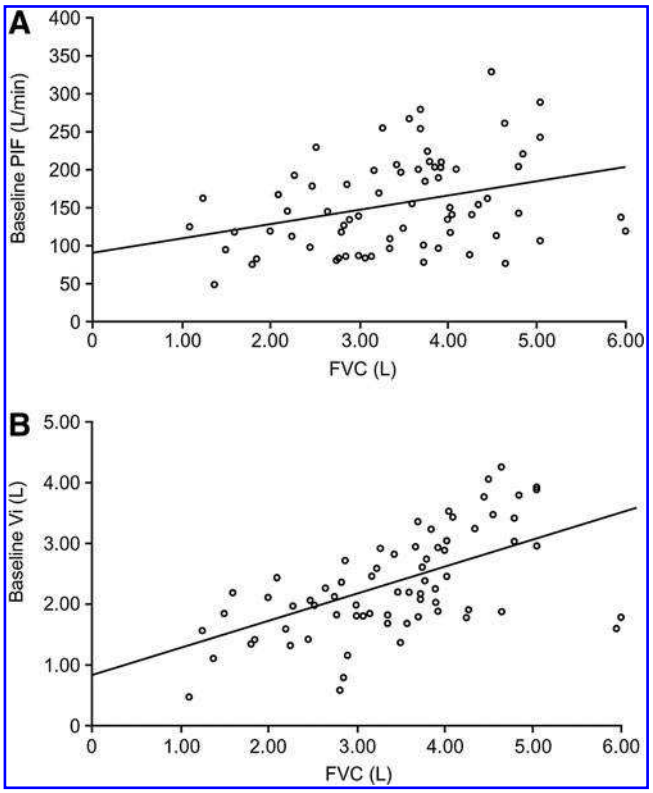

FIG. 4. Correlation of inhalation parameters with FVC. **(A)** Correlation of PIF with FVC ($r = 0.324$; $p = 0.006$). **(B)** Correlation of Vi with FVC ($r = 0.587$; $p < 0.001$).

Although this could be regarded as a potential source of error, patients did not repeat the mistake following instruction to keep the canister depressed. Furthermore, no patient mentioned this possibility as a disadvantage in the open comments. The fact that patients did not repeat the mistake or see this as an issue could be due to the strong feedback mechanism, whereby a halt in airflow following release of the canister would encourage patients to keep the canister depressed for the entire inhalation. Nevertheless, if this coordination cap becomes available for general use, then the importance of keeping the cap depressed will need to be highlighted in the patient information leaflet and included in counseling.

We used a Vi/FVC ratio of >0.6 to indicate a deep inhalation,[15] which was achieved by most patients. Although greater lung deposition of drug occurs when exhaling to residual volume compared with exhaling to functional residual capacity,[11] it has been shown that when using a slow flow, inhalation at different stages of the vital capacity does not affect lung deposition of the drug.[12,28] Receptors for inhaled bronchodilators are distributed throughout the lungs, but bronchodilators have their greatest effect in the conducting airways due to the presence of smooth muscle surrounding the airways.[29,30] Corticosteroid receptors are also present throughout the airways, and inflammation has been shown to exist in all regions of the lungs, especially in asthma.[31] For these reasons, good lung penetration of the aerosol dose is required. Patients should exhale before an inhalation, and the inhalation should continue for as long as possible,[9] but many patients make errors with these two simple steps.[1,3]

Previous correlations of inhalation parameters to spirometry have concentrated on peak inspiratory and expiratory flow and have not been successful.[14,32–34] Our results showed that FVC is a likely predictor of inhalation parameters when patients use an MDI. We did not include FEV_1 because it correlated to FVC, and our preliminary statistical analysis identified FVC rather than FEV_1 as a predictor of inhalation parameters.

Conclusion

A coordination cap together with a simple instruction to lengthen the inhalation time when using an MDI ensures that patients use the recommended slow inhalation flow with good coordination. The coordination cap transforms a traditional MDI into an inhalation co-ordinating device, while the increased resistance to airflow intuitively helps reduce inhalation flow. Training the patient to extend the duration of inhalation also led to reduced inhalation flow. With the cap and simple instructions to inhale for 5 sec, 70% of patients would have achieved the correct MDI technique with respect to coordination and inhalation flow.

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Author Disclosure Statement

W.A., J.C., J.S., and D.S. have no conflicts. H.C. has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with some consultant agreements and honoraria for presentations, from several pharmaceutical companies that market inhaled products. These include AbdiIbrahim, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda, Mundipharma, Omron, Sandoz, Teva, Truddell, and UCB. Research sponsorship has also been received from grant-awarding bodies (EPSRC and MRC).

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